

27. (New) A method of treatment according to claim 26, wherein  
alosetron is in the form of its hydrochloride.

### Remarks

Currently Claims 5-8, and 11-27 are pending. Claims 14 and 18 have been amended to correct an obvious typographical error. New claims 19-27 have been added to complete the record. Support for these claims can be found in Applicants' original specification, particularly at pages 7-12 and Tables 1 and 2.

The title has been amended to be clearly indicative of the invention which is claimed.

### Section 103(a) Rejections Overcome

Claims 5, 8, 11, 14, 15 and 18 currently stand rejected under 35 U.S.C. § 103(a), the Office Action stating that the claims are unpatentable over U.S. Patent No. 5,017,573 to Kon et al. ("Kon"). More specifically, the Office Action states that Kon teaches the administration of indazole-3-carboxylic acid derivatives that are selective antagonists of 5-HT<sub>3</sub> receptors for use in the treatment of IBS. The Examiner acknowledges that the claims differ in that Kon does not distinguish patients who are nonconstipated female IBS patients. The Office Action concludes however, that it would have been obvious to one skilled in the art of gastroenterology to administer the compounds of Kon in each type of IBS, absent evidence to the contrary.

Separately, claims 5-8 and 11-18 currently stand rejected under 35 U.S.C. § 103(a), the Office Action stating that the claims are unpatentable over Bardhan et al., *Gastroenterology* (1996) ("Bardhan"). More specifically, the Office Action states that Bardhan teaches the administration of a highly selective antagonist of 5-HT<sub>3</sub> receptors, alosetron, for the treatment of patients with IBS. The Examiner acknowledges that the claims differ in that Bardhan does not teach other 5-HT<sub>3</sub> antagonists and does not distinguish patients who are nonconstipated female IBS patients. The Office Action concludes however, that it would have been obvious to one skilled in the art of gastroenterology to administer compounds of close structural similarity to alosetron, absent evidence to the contrary.

Applicants respectfully traverse these rejections.

Applicants claims are directed toward methods of treating non-constipated female IBS, diarrhea-predominant female IBS, and symptoms associated with non-constipated female IBS. Applicant's claims are particularly directed toward the treatment of female IBS conditions. The cited references do not disclose or suggest any distinction with regard to the treatment of female IBS conditions versus male IBS conditions.

The rejection is based upon the principle that in the absence of evidence to the contrary one skilled in the art would be motivated to utilize 5-HT<sub>3</sub> antagonists for the treatment of all types of IBS. Applicants respectfully direct the Examiner's attention to pages 7-12 of the instant application, where Applicants have provided evidence to the contrary. The specification includes a detailed description of a study performed in non-constipated (i.e., diarrhea-predominant and alternating ) IBS patients, both males and females. The study demonstrates the unexpected results that 5-HT<sub>3</sub> antagonists produced a much greater beneficial response in female IBS patients than in male IBS patients. The gender disparity among IBS patients noted by the Examiner, does not explain the results reported in the instant specification based on a study conducted in both males and females. The study results clearly demonstrate a much greater beneficial effect in female IBS patients than in males. There is nothing in the cited reference to disclose or suggest to one skilled in the art that such beneficial effects would not be similarly achieved in males.

Further, the inventors of the instantly claimed invention had previously found that 5HT-3 antagonists may cause constipation. In light of this evidence there is no reason for one skilled in the art to expect that 5-HT<sub>3</sub> antagonists could be used to treat all forms of IBS. Applicants' have provided data demonstrating the beneficial effects of 5-HT<sub>3</sub> antagonists such as alosetron in the treatment of non-constipated female IBS. Given the knowledge in the art that IBS may manifest in widely varying symptoms (e.g., diarrhea v. constipation), and the knowledge that 5-HT<sub>3</sub> antagonists may cause constipation, one skilled in the art would not reasonably expect success in the treatment of all forms of IBS with 5-HT<sub>3</sub> antagonists.

Applicants respectfully submit that the instant application is in condition for allowance, which action is respectfully requested. The Examiner is invited to contact the undersigned at 483-8222, to discuss this case further if desired.

Respectfully submitted,



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